

**FINAL TEST PLAN FOR**  
**Tris (4-t-butyl-3-hydroxy-2,6-dimethylbenzyl)**  
**-s-triazine-2,4,6-(1H,3H,5H) trione**  
**(CAS No. 40601-76-1)**

**OVERVIEW**

Cytec Industries Inc. agreed to sponsor tris (4-t-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1H,3H,5H)-trione (CAS No. 40601-76-1) in the U.S. EPA High Production Volume Chemical Program. The sponsor hereby submits a final test plan for this substance. This final test plan makes use of existing measured data, modeling data and newly conducted water solubility and combined reproductive/developmental toxicity screening tests to fulfill screening level data for this chemical. All testing proposed in previous test plans and/or recommended by the EPA has been completed.

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Table 1. Test Plan Matrix for tris (4-t-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (CAS No. 40601-76-1)

<b>CAS No. 40601-76-1</b>	Information	Estimation	Acceptable	New Testing Required
<b>ENDPOINT</b>	Y/N	Y/N	Y/N	Y/N
<b>PHYS/CHEM PROPERTIES</b>				
Melting Point	Y	N	Y	N
Boiling Point	N	Y	Y	N
Vapor Pressure	N	Y	Y	N
Partition Coefficient	Y	Y	Y	N
Water Solubility	Y	N	Y	N
<b>ENVIRONMENTAL FATE</b>				
Photodegradation	Y	Y	Y	N
Stability in Water	Y	N	Y	N
Biodegradation	Y	N	Y	N
Transport between Environmental Compartments (Fugacity)	Y	Y	Y	N
<b>ECOTOXICITY</b>				
Acute Toxicity to Fish	Y	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	N	Y	N
Toxicity to Aquatic Plants	Y	Y	Y	N
<b>TOXICOLOGICAL DATA</b>				
Acute Toxicity	Y	N	Y	N
Repeated Dose Toxicity	Y	N	Y	N
Genetic Toxicity-Mutation	Y	N	Y	N
Genetic Toxicity-Chromosomal Aberrations	Y	N	Y	N
Toxicity to Reproduction	Y	N	Y	N
Developmental Toxicity	Y	N	Y	N
<b>OTHER TOXICITY DATA</b>				
Skin Irritation (NR)	Y	N	Y	N
Eye Irritation (NR)	Y	N	Y	N

Y = yes; N = no; NR = not required

## TABLE OF CONTENTS

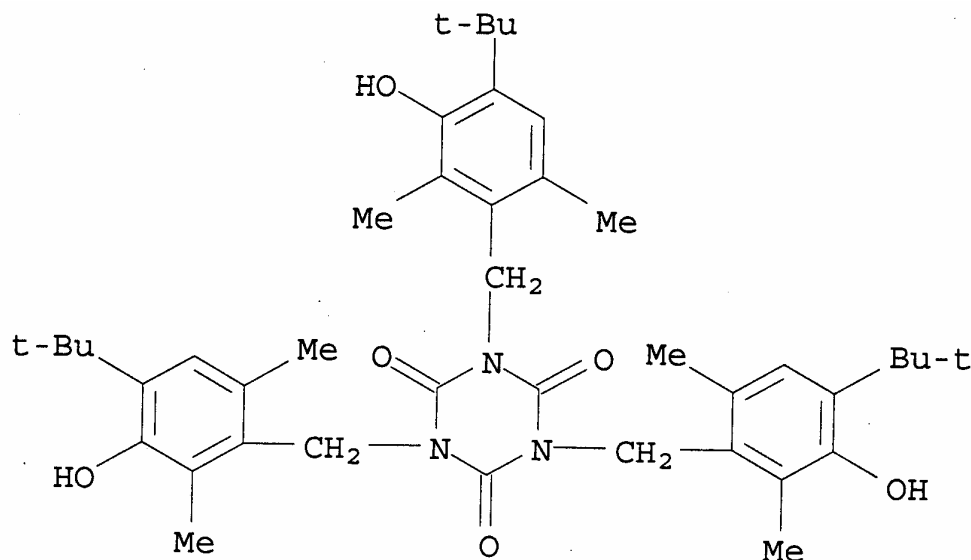
1.	Introduction.....	4
2.	Designation of Test Substance.....	4
3.	General Use and Exposure Information.....	5
4.	Criteria for Determining Adequacy of Data .....	5
5.	Discussion of Available Test Information .....	5
5.1	Chemical and Physical Properties.....	5
5.1.1	Melting Point .....	5
5.1.2	Boiling Point .....	6
5.1.3	Vapor Pressure .....	6
5.1.4	Octanol/Water Partition Coefficient .....	6
5.1.5	Water Solubility .....	6
5.1.6	Summary/Test Plan for Physical Properties .....	7
5.2	Environmental Fate/Pathways .....	7
5.2.1	Photodegradation .....	7
5.2.2	Stability in Water .....	7
5.2.3	Fugacity.....	8
5.2.4	Biodegradation.....	8
5.2.5	Bioconcentration.....	8
5.2.6	Summary/Test Plan for Environmental Fate Parameters.....	8
5.3	Ecotoxicity .....	8
5.3.1	Acute Toxicity to Fish .....	9
5.3.2	Acute Toxicity to Aquatic Invertebrates.....	9
5.3.3	Acute Toxicity to Aquatic Plants.....	9
5.3.4	Summary/Test Plan for Ecotoxicity.....	10
5.4	Human Health Data.....	10
5.4.1	Acute Mammalian Toxicity .....	10
5.4.2	Repeated Dose Mammalian Toxicity.....	10
5.4.3	Genetic Toxicity.....	12
5.4.4	Reproductive and Developmental Toxicity .....	12
5.4.5	Additional Data.....	13
5.4.6	Summary/Test Plan for Mammalian Toxicity .....	13
6.	Summary .....	14
7.	References.....	14

## 1. Introduction

Cytec Industries Inc. agreed to supply hazard and exposure information under The U.S. EPA High Production Volume Chemical Program for tris(4-*t*-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (CAS No. 40601-76-1). The initial test plan and robust summaries were posted on the EPA website on October 15, 2003. A revised test plan and summaries were posted on August 24, 2004. That plan indicated that testing for the following endpoints would be conducted: water solubility and reproductive/developmental toxicity (OECD Test Guideline 421). Testing for the aforementioned endpoints has been completed, and the current test plan (and accompanying robust summary document) communicates their results (in addition to data previously submitted). Testing that has been performed fulfills all requirements of the HPV program; therefore this test plan and robust summary document are considered final.

## 2. Designation of Test Substance

The test substance presented in this test plan is tris(4-*t*-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (CAS No. 40601-76-1). It is a free-flowing white powder, with a molecular formula of C<sub>42</sub>H<sub>57</sub>N<sub>3</sub>O<sub>6</sub>. Its chemical structure is as follows:



This substance has the following synonyms:

1,3,5-tris[[4-(1,1-dimethylethyl)-3-hydroxy-2,6-dimethylphenyl]methyl]-  
1,3,5-tris[[4-tert-butyl-3-hydroxy-2,6-dimethylphenyl]methyl]-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione  
1,3,5-tris(2,6-dimethyl-3-hydroxy-4-tert-butyl) isocyanurate

It also appears as a commercial product under the Cytec Industries Inc. trade name of CYANOX® 1790 Antioxidant. According to the MSDS, the purity of this material is 93.7-98.9%.

### **3. General Use and Exposure Information**

Tris(4-t-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1H,3H,5H)-trione is produced by Cytec Industries Inc. in a closed system of reactors, centrifuges and driers. Local exhaust and dust collection are provided at the packaging stations. Under prescribed conditions of end use, which include the use of adequate ventilation and personal protective equipment, there should be minimal worker exposure. Tris(4-t-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1H,3H,5H)-trione is an effective antioxidant for a variety of polymer systems. This substance provides superior polymer stabilization with minimal color contribution and low volatility. The substance may be used in food packaging materials and polystyrene and rubber modified polystyrene as an antioxidant. As such, it is cleared by the FDA under 21 CFR (Code of Federal Regulations) Section 178.2010. The material is also used as an antioxidant in polyethylene polymer, at the 0.05-0.10% level. The substance is melt-soluble in the polymer, and therefore migration from the polymer is limited. The material is also used as an antioxidant in fiber (such as Spandex® PUR fiber) at the 0.5-1.5% level.

### **4. Criteria for Determining Adequacy of Data**

All available studies were reviewed and assessed for adequacy according to the standards of Klimisch et al. (1997). Studies receiving a Klimisch rating of 1 or 2 were considered to be adequate.

### **5. Discussion of Available Test Information**

The test plan matrix (as shown in Table 1 on page 2) was constructed after a careful evaluation of all existing data (see below). This matrix is arranged by study type (columns) and screening data endpoints (rows), and indicates if data are provided for each end point in the sets of robust summaries.

#### **5.1 Chemical and Physical Properties**

The results of chemical/physical property testing are shown in Table 2.

##### **5.1.1 Melting Point**

A melting point of 159-162 °C is available (Cytec Industries Inc., 2001).

Table 2. Chemical/physical properties of tris (4-t-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione

Endpoint	Value
Molecular weight grams/mol	699
Melting point	159-162 °C
Boiling point	926 °C*
Relative density	No data
Vapor pressure	0.000013 hPa*
Partition coefficient (Log Pow or Kow)	15.281*
Water solubility (mg/l)	< 0.02 mg/l

\* Estimated using EPIWIN

### 5.1.2 Boiling Point

EPIWIN Mpbpwin was used to estimate a boiling point of 926°C based on the structure of the molecule and a measured melting point of 160.5°C. The EPIWIN value is probably not accurate, since nearly all organic molecules decompose well below this temperature. Nevertheless, the high melting point, together with the EPIWIN estimate and the very large size of the molecule, which lacks functional groups known to contribute to volatility, supports the conclusion that the boiling point is very likely to be above 300°C.

### 5.1.3 Vapor Pressure

No measured vapor pressure data are available for this substance. EPIWIN Mpbpwin was used to estimate a vapor pressure of approximately 0.000013 hPa, based on the structure of the molecule and a measured melting point of 160.5°C. This estimate, combined with the observations made in Section 4.1.2 pointing to a boiling point above 300°C, is sufficient to characterize the test substance as having a vapor pressure well below 0.001 hPa.

### 5.1.4 Octanol/Water Partition Coefficient

EPIWIN Kowwin has been used to estimate a log Kow of 15.281. This highly positive value is consistent with the high molecular weight, aromatic, non-polar molecular structure and is sufficient to characterize this endpoint.

### 5.1.5 Water Solubility

EPIWIN Wskow predicts that this substance has very limited water solubility ( $2.425 \times 10^{-11}$  mg/l), which is consistent with the very large size of the molecule, its multiple aromatic rings and alkyl side chains (which are hydrophobic), and the absence of polar functional groups that would contribute significantly to water solubility. In addition, as agreed upon in the revised test plan,

the sponsor has conducted an OECD Test Guideline 105 water solubility determination, which confirms that the test substance indeed has a very limited water solubility of < 0.02 mg/l at 20 °C (O'Conner and Mullee, 2004).

### 5.1.6 Summary/Test Plan for Physical Properties

As agreed, testing has been conducted to obtain a measured value for water solubility. The results confirm that the material has limited water solubility. Adequate data now exist to fill all required endpoints for physical properties.

## 5.2 Environmental Fate/Pathways

Results of environmental fate modeling and studies are summarized in Table 3.

Table 3. Environmental fate parameters for tris (4-t-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione

Endpoint	Value
Indirect Photolysis (OH sensitizer) (Hydroxyl Radical Rate Constant) * (Atmospheric T <sub>1/2</sub> ) *	9.08947 E-11 cm <sup>3</sup> /molecule-sec 1.4 hours
Stability in Water *	T <sub>1/2</sub> > 1 year
Henry's Law Constant *	1.7E-27 atm-m <sup>3</sup> /mol
Koc *	1E+10
Bioconcentration Factor (log BCF) *	0.500
Environmental transport (Fugacity Level III mass percentages) *	Air = 0 Water = 1.28 Soil = 31.6 Sediment = 67.1
Biodegradation	25.9% biodegraded in 28 days (not readily biodegraded)

\* Estimated using EPIWIN

### 5.2.1 Photodegradation

Photodegradation with hydroxyl radical sensitizer was estimated using EPIWIN/Aop (v1.90). An overall hydroxyl radical rate constant of 9.08947 E-11 cm<sup>3</sup>/(molecule\*sec) was calculated based on the summation of individual rate constants for each bond fragment in the molecule using the program algorithm. A half-life of 1.4 hours was calculated assuming a constant concentration of OH radical and pseudo first order kinetics. Atmospheric photodegradation is not expected to be a significant elimination pathway, since this substance has limited volatility.

### 5.2.2 Stability in Water

EPIWIN Hydrowin predicts that the rate of hydrolysis of the material in neutral water at ambient temperatures will be extremely slow, with a half life of > 1 year. This estimate is based on the presence of urea functional groups in the molecule. No other functional groups in the molecule (including the phenolic function) are expected to be subject to hydrolysis. In addition, the very limited water solubility of this substance further reduces the potential for hydrolysis.

### 5.2.3 Fugacity

Level III fugacity modeling has been conducted on the test material using the EPIWIN model. Inputs to the program are CAS No. 40601-76-1, and a melting point of 160.5 °C. Emission rates inputted into the program were air: 0 kg/hr, water: 1000 kg/hr, soil: 1000 kg/hr and sediment: 0 kg/hr. The following half-lives were calculated:  $T_{1/2}$  air = 2.82 hr, water = 3600 hr, soil = 3600 hr, and sediment = 14400 hr. A Henry's Law Constant of  $1.7E-0027$  atm-m<sup>3</sup>/mol and a soil sediment partition constant ( $K_{oc}$ ) of  $1E+10$  were estimated using the EPIWIN/Henry and Pckoc Programs, respectively. The percent mass balances predicted for this substance in air, water, soil and sediment are shown in Table 3. As shown, the majority of the material partitions to soil and sediment.

### 5.2.4 Biodegradation

Results of an OECD Test Guideline 301 B, Ready Biodegradability: Modified Sturm Test (CO<sub>2</sub> evolution) show that Cyanox 1790 is biodegraded to some extent by wastewater bacteria (25.9% after 28 days), but is not readily biodegraded (Baldwin, 2002). This test was assigned a reliability rating of 2, and is considered to be adequate. However, it is possible that this test underestimates the ability of the material to biodegrade since the concentration used was toxic to the bacteria and greater than the solubility limit.

### 5.2.5 Bioconcentration

A bioconcentration factor was calculated using the EPIWIN BCF Program ( $\log BCF = 0.5$ ).

### 5.2.6 Summary/Test Plan for Environmental Fate Parameters

Estimated values are available for the hydroxyl radical induced photolysis rate constant and atmospheric half-life, Henry's Law Constant, soil sediment partition coefficient, Fugacity Level III environmental transport parameters and bioconcentration factor. No further testing is planned for these endpoints. No testing is planned for water stability (hydrolysis) because this material does not have functional groups known to be easily hydrolyzed under neutral ambient conditions and has very limited solubility in water. The existing biodegradation study is considered to be adequate; therefore no additional biodegradation studies are planned.

## 5.3 Ecotoxicity

Tris(4-t-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione is not expected to be a hazard to aquatic species, since the material has very limited water solubility (< 0.02 mg/l). Therefore, aquatic toxicity testing for this material is not considered to be relevant.

Nevertheless, studies have been performed in fish and Daphnia to characterize the toxicity of the material at its solubility limit.

### **5.3.1 Acute Toxicity to Fish**

A static OECD Test Guideline 203 limit study in juvenile rainbow trout was performed with Cyanox 1790 (Glover, 2002a). The no observable effect concentration (NOEC) and lethal concentration in 50% of the organisms (LC<sub>50</sub>) in this 96-hour study were 100 and > 100 mg/l, respectively. None of the fish exposed to the highest concentration tested (100 mg/l) died or exhibited signs of toxicity by 96 hours. This study was given a reliability rating of 2 (valid with restrictions) since concentrations of test material were not analytically confirmed. In this study, the actual concentration used was the amount of material that remained in solution after the mixture containing 100 mg/l was filtered. Therefore, the concentration that was used was actually the solubility limit of the test material in the medium at 15 °C. An OECD Test Guideline 105 water solubility study confirms that Cyanox 1790 has a water solubility of < 0.02 mg/l at 20 °C. Accordingly, the actual concentration of material that the rainbow trout were exposed to in the OECD study approximates this value. Since the material was not toxic to rainbow trout at the solubility limit, it is not expected to be toxic to fish at environmentally relevant concentrations.

### **5.3.2 Acute Toxicity to Aquatic Invertebrates**

A static OECD Test Guideline 202 limit study in Daphnia was performed with Cyanox 1790 (Glover, 2002b). The no observable effect concentration (NOEC) and lethal concentration in 50% of the organisms (LC<sub>50</sub>) in this 48-hour study were 1000 and > 1000 mg/l, respectively. In this study, 10% of the organisms exposed to the highest concentration tested (1000 mg/l) died by 48 hours. Since the mortality rate in the controls also was 10%, the deaths of Daphnia exposed to the test material were not considered to be treatment-related. This study was given a reliability rating of 2 (valid with restrictions) since concentrations of test material were not analytically confirmed. In this study, the actual concentration used was the amount of material that remained in solution after the mixture containing 1000 mg/l was filtered. Therefore, the concentration that was used was actually the solubility limit of the test material in the medium at 20 °C (< 0.02 mg/l). Accordingly, the actual concentration of material that the Daphnia were exposed to in the OECD study approximates this value. Since the material was not toxic to Daphnia magna at the solubility limit, it is not expected to be toxic to aquatic invertebrates at environmentally relevant concentrations.

### **5.3.3 Acute Toxicity to Aquatic Plants**

Testing for toxicity to aquatic plants has not been performed. However, no testing is necessary, (as agreed upon in previous correspondence with the EPA), since the material is virtually insoluble in water (measured solubility of < 0.02 mg/l). Since the EC50 value for algal toxicity predicted by EPIWIN-modeling ( $6.14\text{E}^{-10}$  mg/l) is higher than the EPIWIN-predicted solubility of  $2.425\text{E}^{-11}$  mg/l, the material would not be expected to be toxic to algae at the solubility limit.

### 5.3.4 Summary/Test Plan for Ecotoxicity

Results of adequate studies in rainbow trout and *Daphnia magna* show that tris(4-*t*-butyl-3-hydroxy-2,6-dimethylbenzyl)-*s*-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione is not toxic to these species at the solubility limit. Although a test to assess toxicity to aquatic plants has not been performed, such a test is not necessary due to the virtual insolubility of the test material, and EPIWIN-predicted lack of toxicity to algae at the solubility limit.

## 5.4 Human Health Data

### 5.4.1 Acute Mammalian Toxicity

This endpoint is filled by a sufficient oral toxicity study in rats and an additional dermal study in rabbits (Carpenter, 1973). The oral and dermal LD<sub>50</sub> values (lethal doses in 50% of the animals) for Cyanox 1790 were greater than the highest dose tested (10,000 and 5,000 mg/kg, respectively). These concentrations also did not cause any signs of toxicity. The LC<sub>50</sub> value for aerosol inhalation in a poorly described study was also greater than the highest dose tested (20 mg/l).

### 5.4.2 Repeated Dose Mammalian Toxicity

Sufficient oral, repeated dose toxicity tests have been conducted in both rats and dogs. The results are summarized in Table 4.

Ninety or ninety-one day feeding studies have been conducted with Cyanox 1790 in rats and dogs. The no observable affect levels in these studies were greater than the highest doses tested (400 and 46 mg/kg/day, respectively). Clinical signs such as diarrhea, soft stools, or encrustment of the nares were noted in some animals treated with the test material. Study personnel attributed these signs to ingestion of a powdered food and did not consider them to be related to test material. The clinical chemistry findings in rats and dogs treated with Cyanox 1790 for 90-91 days (ie. elevated gamma-glutamyl transpeptidase in high dose male rats, decreased glutamic-oxaloacetic transaminase in female dogs, decreased glucose in female rats and male and female dogs, increased red blood cell counts in mid-dose male rats and decreased red blood cell counts in male dogs) were not considered to be related to test material since they were not dose-dependent and were within normal limits. Study personnel also did not consider the reduced body weight gains in female dogs treated for 90 days with 7.5, 15 or 30 mg/kg/day to be related to test material because 1) food consumption was comparable between groups and 2) no abnormal clinical signs were noted. Reduced food consumption in female dogs treated with 46 mg/kg/day test material for 90 days also was not considered to be relevant since no other effects were noted.

In a 30-day study in beagle dogs, administration of up to 1600 mg/kg/day was not associated with increased lethality. Concentrations of test material  $\geq$  100 mg/kg/day were associated with marked histopathological changes in the liver. The dose at which liver toxicity was first noted is difficult to determine due to the fact that higher concentrations of test material than desired were administered to the animals during the latter part of the study. The lowest observable effect level

Table 4. Repeated Dose Toxicity of Cyanox 1790

Species/ Exposure	Dose <sup>a</sup> (deaths)	Gross Changes	Histopathological Changes	Clin. Chem/Hemat. Changes
SD rat, 90 days, oral feed (Miller, 1977a)	25 (0) 100 (1) 400 (0) <sup>b</sup>	alopecia, diarrhea, encrustment around nares same as above same as above	none none mononuclear leukocyte infiltration in the liver (N = 1)	none ↑rbc, ↓ glucose ↓ glucose, ↑ GGTP
Beagle dog, 91 days, oral feed (Miller, 1977b)	7.5 (0) 15 (0) 30 (0) <sup>b</sup>	soft stool, ↓ bw (females) same as above same as above	none none none	↓ glucose, GOT ↓ glucose, rbc ↓ glucose, GOT
Beagle dog, 91 days, oral feed (Procter et al., 1983)	46 (0) <sup>b</sup>	↓ food in females	none	none
SD rat, 30 days, oral feed (McElroy and Ward, 1976)	0.5 % (0) 1.0 % (0) 2.0 % (0) <sup>b</sup>	diarrhea, ↑ liver weight skin irritation diarrhea, skin irritation. ↑ food, ↓ bw (females)	none none changes in liver (N = 1 male)	not determined not determined not determined
Beagle dog, 30 days, oral feed (Upman and Ward, 1976) <sup>c</sup>	25-84 (0) 100 - 333 (0) 400 <sup>d</sup> - 1335 (0) 1600 (0)	soft feces soft feces soft feces, ↓ bw, food, ↑ kidney wt. soft feces, ↓ bw, food, ↑ liver, kidney, adrenal wt.	mild - moderate changes in liver marked changes in liver marked changes in liver marked changes in liver	not determined not determined not determined not determined

GGTP = gamma-glutamyl transpeptidase; GOT= glutamic-oxaloacetic transaminase

<sup>a</sup> Dose is in mg/kg unless listed otherwise; <sup>b</sup> No effect level assigned to study; <sup>c</sup> Study was assigned a reliability rating of 4; <sup>d</sup> Low effect level assigned to study

assigned by study personnel was 400 mg/kg/day. However, since all doses appeared to cause histological changes in the liver, the LOAEL appears to be lower than the lowest dose tested (25 mg/kg for 3 weeks, followed by 84 mg/kg for 9 days).

Results of the OECD Test Guideline 421 study that was recently conducted (see Section 4.4.4) indicate that repeated, dietary exposure of up to 1000 ppm (approximately 70 mg/kg/day) Cyanox 1790 for 15-28 days or 40-53 days is well-tolerated in male and female rats (respectively). Concentrations of 10000 and 20000 ppm (782 and 1558 mg/kg/day) caused severe skin irritation resulting in scabbing and fur loss on the top of the head and/or around the snout of all females. Similar findings were noted in 3/10 males treated with 20000 ppm (1294 mg/kg/day). However, there was no effect of treatment of up to 20000 ppm on body weight, food consumption, weights of epididymides and testes, gross pathology, or histopathology of selected organs (coagulating glands, epididymides, prostate, seminal vesicles, testes, pituitary, ovaries, uterus/cervix or vagina).

### **5.4.3 Genetic Toxicity**

#### **5.4.3.1 Mutagenicity**

Tris(4-t-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione has been tested for mutagenicity in an OECD Test Guideline 471 (bacterial mutagenicity) study conducted with *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2uvra- (Krul and Ommen, 2001), and in an OECD Test Guideline 476 (mammalian cell mutagenicity) study conducted with cultured mouse lymphoma L5178Y cells (Steenwinkel, 2001). Results of both tests were negative.

#### **5.4.3.2 Chromosomal aberration**

A mouse micronucleus study has been conducted according to GLP with concentrations of tris (4-t-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione up to 5,000 mg/kg (Guenard, 1983). In this test, there was no significant difference between the numbers of micronucleated polychromatic (PCE) or normochromatic erythrocytes (NCE) in treated animals versus vehicle-treated controls.

The material also has been tested for its ability to cause chromosomal aberrations in an OECD Test Guideline 473 study performed with cultured Chinese Hamster Ovary Cells (CHO K-1 line) (deVogel, 2001). In two separate tests, there was no significant effect of the test material on the number of cells with aberrations (with and without metabolic activation). In both of the tests, the highest concentration of test material used (250 micrograms/ml) did not cause the desired degree of inhibition of the mitotic index (50-70%). However, higher concentrations could not be tested due to insolubility.

### **5.4.4 Reproductive and Developmental Toxicity**

Since the effect of Cyanox 1790 on development had not been previously assessed, an OECD Test Guideline 421 study was conducted in rats (Knox et al., 2005). Sprague Dawley rats (10/sex/dose) were given 0, 1000, 10000 or 20000 ppm Cyanox 1790 in the diet (69, 651 and 1294 mg/kg/day in males and 77, 782 and 1558 mg/kg/day in females) 14 days prior to mating (males and females), up to 13 days during mating (males and females), during gestation (females only), and to day 5 of lactation (females only). The NOAELs for systemic, reproductive and developmental toxicity were 1000, 10000 and 20000 ppm, respectively. Ingestion of 10000 and 20000 ppm was associated with signs of severe skin irritation on the heads of maternal animals. There was no effect of ingestion of up to 20000 ppm test material on maternal or paternal body weight or food consumption, weights of the testes or epididymis, histopathology of reproductive organs, or any index of fertility or developmental toxicity measured (with the exception of increased post-implantation loss and a corresponding decrease in litter size at 20000 ppm).

The increased post-implantation loss in the aforementioned study is likely due to maternal toxicity and/or stress from exposure to a severely irritating test material, which was not detected by the limited scope of analyses performed in the screening-level study. The effects of maternal toxicity on embryofetal survival and development have been reviewed by Khera et al. (1985),

who found a "fairly strong" association between embryo-fetal mortality (post-implantation loss) and maternal toxicity (significant reduction in weight gain, test agent-related pharmacologic or toxicologic signs of behavior, abortion or death) in an analysis of data from studies in hamsters, mice, rats and rabbits. Embryo-fetal deaths and maternal toxicity were co-reported in 133/177 (75%) of the studies and embryo-fetal deaths at doses causing no apparent maternal toxicity were reported in only 9/140 (6%) of the studies.

In agreement with the OECD Test Guideline 421 study, results of ninety or ninety one day, repeated dose oral studies in rats and dogs indicate that the material has no effect on histopathology of male (prostate, testes, epididymides or seminal vesicle) or female (uterus, ovaries, or vagina) reproductive organs at concentrations up to 400 mg/kg/day and 46 mg/kg/day, respectively (Miller, 1977b; Procter et al., 1983).

#### **5.4.5 Additional Data**

##### **5.4.5.1 Skin and Eye Irritation**

Results of a modified Draize-Shelanski Repeat Insult Patch Test in humans show that administration of 2.5% Cyanox 1790 in petrolatum is not irritating to skin (Kligman, 1976). Administration of 100 mg solid test material also is not irritating to rabbit eyes (Carpenter, 1973).

##### **5.4.5.2 Sensitization**

Results of a modified Draize-Shelanski Repeat Insult Patch Test conducted in one hundred healthy adults indicate that 2.5% Cyanox 1790 in petrolatum is not sensitizing to human skin (Kligman, 1976).

#### **5.4.6 Summary/Test Plan for Mammalian Toxicity**

Adequate studies with tris(4-t-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione have been conducted for all endpoints. Acute oral, inhalation and dermal studies show that acute exposure to fairly large amounts of the material is required to cause lethality or symptoms of toxicity. Neat material is not irritating to eyes and 2.5% Cyanox 1790 in petrolatum is not irritating or sensitizing to skin. Results of adequate 90-day repeated dose studies show that dietary exposure to 400 or 46 mg/kg/day does not cause toxicity to rats or dogs, respectively. Dietary exposure to concentrations greater than 100 mg/kg/day for 30 days is associated with liver toxicity in dogs. Adequate studies in vivo and in vitro show that tris(4-t-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione is not mutagenic or clastogenic.

An OECD Test Guideline 421 study in male and female rats indicate that dietary exposure of up to 20000 ppm tris (4-t-butyl-3-hydroxy-2,6-dimethylbenzyl)-s-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (1294 mg/kg/day in males and 1558 mg/kg/day in females) prior to mating and during gestation and lactation does not cause reproductive organ or developmental toxicity. However, this dosing regimen is associated with severe facial/head skin irritation and increased post-implantation loss

in maternal animals (with a corresponding decrease in litter size). The NOAELs for skin irritation and increased post-implantation loss were 1000 (69 and 77 mg/kg/day in males and females) and 10000 ppm (651 and 782 mg/kg/day in males and females), respectively. It is believed that the increased post-implantation loss at 20000 ppm was likely due to maternal toxicity and/or stress from exposure to a severely irritating test material, which was not detected by the limited types of assays performed in the screening-level study.

## **6. Summary**

### Physical properties

Adequate data are available for melting point, boiling point, vapor pressure, partition coefficient and water solubility. No further testing is planned for physical property endpoints.

### Environmental fate properties

Adequate data are available for all environmental fate endpoints. EPIWIN modeling provides adequate data for hydroxyl radical induced atmospheric photodegradation and environmental transport, as well as bioconcentration factor and Henry's Law Constant. The material does not have functional groups known to be easily hydrolyzed under neutral ambient conditions, and has very limited solubility in water. An OECD Test Guideline biodegradation study shows that the material is biodegradable (albeit not readily).

### Aquatic toxicity

Tests that have been performed with rainbow trout and Daphnia indicate that the material is not toxic to these species at the highest obtainable dissolved concentration. Since the water solubility of the material is extremely low and the ECOSAR-estimated EC<sub>50</sub> value is greater than this value, the material would not be expected to be toxic to algae at environmentally relevant concentrations. Therefore, no testing in algae is necessary.

### Mammalian toxicity

No additional mammalian testing is planned since adequate tests have been performed for all mammalian toxicity endpoints. The material is of low acute toxicity and is not mutagenic or clastogenic. The NOAELs in 90-day repeated dose dietary studies are 400 and 46 mg/kg/day in rats and dogs, respectively. In an OECD Test Guideline 421 study, severe facial/head skin irritation and increased post-implantation loss were noted in female rats ingesting > 650 and > 1200 mg/kg/day in the diet (respectively), prior to mating and during gestation and lactation.

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